The Board has agreed that the specification are enabling and that there is no need of undue experimentation for administering a composition comprising a soluble peptide containing a portion of amino acid 1-136 of SEQ ID NO:2 to modulate an immune response in vivo (Decision p.13). The Board disagrees with respect to a polypeptide mimetic thereof of SEQ ID NO: 2 (Decision p. 12 and 13 and DRR p.4). We have amended as follow:

1) We have amended claim 1 by deleting the language "polypeptide mimetic" and we have updated the language according to the Board's decision "a composition comprising a soluble polypeptide".

2) We have added the language "fragment, or an equivalent" to be in accordance with our specifications. The word fragment is defined and supported by paragraphs [0055] and [0073]. The word equivalent is extensively defined in paragraphs [0035], [0073], [0075], [0105] and the biological structures of the polynucleotides mentioned are also described in the section Polynucleotides including the paragraphs [57] to [68] and refer also to the Section Polypeptides including the paragraphs [69 to [81]. Moreover, the claim of equivalent is in accordance with rev. 8 of MPEP Chapter 2100, Section 2181, p. 240 as stated ("An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and **equivalents** thereof."). The Applicants state that even though the phrase "means for" or "step for" is not used, the claim limitation is written as a function to be performed and does recite only a limited amount of structure to qualify for claiming equivalent under 35 U.S.C. 112, sixth paragraph.

3) We have amended claim 1 to include all of SEQ ID NO: 2 in conformity with our specifications.

4) We have amended claim 3 to be in exact conformity with our specifications as found in parag. [0073] as follow: " ...fragments, having the amino acid sequence of the TREM-1 splice variant polypeptide of SEQ.ID.NO: 2, in which several, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid residues are substituted, deleted or added, in any combination."

5) We have amended claim 11 to be in accordance with claims 1 and 3.

6) And we have amended claim 40 to be complete and according to our specification parag. [0033].

B. The second objection remaining is whether Claims 1, 3, 5, 11, 15, 16 and 40-42 are anticipated by the disclosures of U.S. patent no. 6,420,526 by Reuben under the meaning of 35 U.S.C. § 102(e).

The applicants believe that Claims 1, 3, 5, 11, 15, 16 and 40-42 are not anticipated by the disclosures of US patent no. 6,420,526 by Reuben for the following reasons.

1) The two molecules have different sequences and thus are not the same. A basis of the rejection is the apparent similarity of the sequence SEQ ID NO: 478 and SEQ ID NO: 2 of this application. The Board has acknowledged the difference (DRR p.4) while still missing an important point. SEQ ID NO: 2 from Applicants' specification is found in Figure 4 and is defined as being the amino acid sequence of TREM-1sv as defined in specifications [56] and [60]. More specifically in Figure 4, TREM-1sv is the lower amino acid sequence presented. It contains only 150 amino acids because of a deletion from amino acid 136 to 200 that is coding for the transmembrane portion of TREM-1. Moreover, it has a distinct addition of 15 amino acids from 136 to 150. This sequence with the deleted portion and a

new addition corresponds to TREM-1sv and is SEQ ID NO: 2. Reuben's SEQ ID NO: 478 contains 234 amino acids because it does not contain this deletion (see APPENDIX II, Reuben's SEQ ID NO: 478) and does not contain the distinct addition of SEQ ID NO: 2. It is similar to the TREM-1 sequence or the upper sequence of amino acids presented in Figure 4. Sequence comparison between SEQ ID NO: 2 or TREM-1sv and Reuben's SEQ ID NO: 478 or TREM-1 shows that SEQ ID NO: 2 has a composition different from Reuben's, making it a different molecule with different properties such as solubility and thus allowing different usage as well.

2) The method of use in each invention is different. The present invention teaches the administration of a composition of soluble polypeptides whereas Reuben's invention teaches the administration of a polypeptide. Administering a polypeptide versus administering a soluble polypeptide is significantly different as shown by the mechanism of action of each invention that is distinct. Reuben's method would not work in the present invention. In our method, we administer a composition of soluble polypeptides to capture TREM-1 ligand because there is a requirement for solubility of the polypeptide for this mechanism to work. As recognized by the Board, Reuben did not identify that mechanism (DRR p.5) and consequently his method is not adequate to fulfill the characteristic TREM-1 ligand binding modulation of the immune system. In order to do so, the polypeptide must be soluble to travel in the body and capture the ligand before it reaches TREM-1 as described in our specification parag. [101]. If the polypeptide is not soluble it will not bind TREM-1 ligand and it won't travel to find that ligand. Therefore, there can be no anticipation that Reuben's peptides can fulfill that purpose because the solubility requirement present in our method as well as the teaching of modulating the immune response through the TREM-1 pathway are absent from Reuben's specification.

3) The immunological mechanism targeted by the method used in each invention is different.

Reuben claims a series of EST sequences of which he claims that administration of their correspondent peptides can modulate the immune system through the antigen-antibody network of immune regulation involving T cells. In contrast, Applicants claim invention of a therapeutic method including the use of a composition of soluble peptides according to sequence of SEQ ID NO: 2 for modulating the immune system specifically through the monocyte TREM-1 receptor ligand binding activity.

Reuben teaching is based on similarity with the heavy chain of immunoglobulin (Ig) and their binding function as stated in Decision, FF19. Igs have been known to bind a wide variety of antigens long before Reuben and this is a teaching different from the one of the distinctive macrophage receptor of activation TREM-1 binding to its specific ligand such as the teaching of Applicant's specification. Reuben does not teach anything in regard to the TREM-1 receptor ligand complex but rather antigens binding to antibody-like structure. Second and not the least, Reuben's specification column 139 in "Feature of Protein Encoded by Gene No: 159 "teaches that "This gene is expressed primarily in activated neutrophil and to a lesser extent in activated T cell, monocytes, and heart." The Applicants' invention teaches that TREM-1 receptor is expressed exclusively on myeloid cells, defined as being macrophages and neutrophils (Applicants' specification paragraph [6]). TREM-1 receptor is not on T cells, defined as lymphoid cells and is not on heart cells as both thought by Reuben. Exclusive expression on myeloid cells is the reason for the origin of its name TREM-1 (Triggering Receptor Expressed on Myeloid-1) as defined by Bouchon et al., in REFERENCES of the specification. Moreover, the Applicants teach that the specific complex TREM-1 receptor-ligand is known to trigger the TREM-1 receptor present on macrophages and to activate them. And the binding of TREM-1sv or a soluble peptide with

the same biological binding activity to that specific TREM-1 ligand can modulate the immune response through macrophage regulation of activation. In contrast, Reuben teaches a molecule with the natural binding activity of Ig that can bind a large variety of common antigens that may modulate the immune response through the antigen-antibody network of immunoregulation. He does not teach regulation of the immune system through the macrophage TREM-1 ligand complex-receptor. In that respect, using a composition of soluble polypeptides such as in the present invention versus Reuben's administration of a peptide where there is no teaching of requirement for solubility are two different inventions because Reuben's method as described in his specifications would not work through the TREM-1 pathway. Evidently, each method is different because it targets a different mechanism of action. And distinction between the teachings and methods of each invention is supported by the fact that there is neither data nor evidence that TREM-1 ligand is a common antigen. In fact, recent data suggest that it is a receptor expressed by platelets (Haselmayer et al. Blood 110:1029, 2007, copy enclosed) supporting our point that this invention's teaching of the specific TREM-1 receptor and TREM-1sv ligand binding activity is substantially different from Reuben's anticipated molecule with Ig like binding activity for a variety of common antigens and which is expressed also on T cells.

In that regard, the Applicants claim and present validation of biological activity for soluble portion of sequence of SEQ ID NO: 2 and for its usage in the treatment of conditions that can benefit from capturing that specific TREM-1 receptor binding ligand with TREM-1sv or derived peptides before it reaches the myeloid expressed TREM-1 activating receptor. The Applicants state that their specification and claims are the results of experimentations conducted that lead to the discovery of TREM-1sv (specification, Figure 2 and also Gingras et al., Molecular Immunology 38:817, 2001, copy enclosed) and they assert that their specification teaches a distinct method involving administration of a soluble polypeptide to

modulate the immune system, that is not anticipated nor described by Reuben's, for the treatment of conditions that can benefit from capturing the specific TREM-1 receptor binding ligand.

Therefore, based on the facts that 1) SEQ ID NO: 498 and SEQ ID NO: 2 are two different molecules, 2) the method of use of each invention is different as evidenced by their respective targeted mechanism of immune modulation and 3) the mechanism of immune modulation targeted by each invention is distinct, the Applicants believe that the rejection anticipated by Reuben should be reversed.

CONCLUSION

The Applicants believe that in light of the new amendments and of the above clarifications about the difference between the two inventions, the remaining rejections are overcome and the amended claims now meets condition of allowance.

Respectfully submitted,

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APPENDIX I (Tracked changes of amended claims 1, 3 and 11)

1. (Amended) A method of modulating an immune response including ~~comprising~~ administering to an animal, in need thereof, a composition comprising a ~~of~~ soluble polypeptides, a fragment, or an equivalent ~~with at least a portion of amino acids 1 to 136 of~~ according to SEQ ID NO: 2, ~~or a polypeptide mimetic thereof,~~ in an amount effective to modulate the levels of TREM-1 and /or ligand binding activity whereby the immune response is modulated in the animal.

3. (Amended) The method of claim 1, wherein said polypeptide, fragment or equivalent according to SEQ ID NO: 2 can have several additions, deletions, fusions and/or substitutions of amino acids in any combination. ~~has at least a portion of amino acids 36 to 114 of SEQ ID NO: 2, the whole portion of amino acids 36-114 of SEQ ID NO:2, or more than the whole portion of amino acids 36-114 of SEQ ID NO:2.~~

11. (Amended) The method of claim 1 or 3, wherein said polypeptide, fragment, or equivalent are ~~is~~ admixed with a pharmaceutical carrier.

APPENDIX II Reuben's SEQ ID NO: 478

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SEQ ID NO 478
LENGTH: 284
TYPE: PRT
ORGANISM: Homo sapiens
SEQUENCE: 478

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Met Arg Lys Thr Arg Leu Trp Gly Leu Leu Trp Met Leu Phe Val Ser
 1               5                  10                  15
Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu Lys Tyr Glu Leu Lys
            20                  25                  30
Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr Thr Leu Glu Lys Phe
        35                  40                  45
Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg Asp Gly Glu Met Pro
    50                  55                  60
Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys Asn Ser His Pro Val
65                  70                  75                  80
Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr His Asp His Gly Leu Leu
                85                  90                  95
Arg Val Arg Met Val Asn Leu Gln Val Glu Asp Ser Gly Leu Tyr Gln
            100                 105                 110
Cys Val Ile Tyr Gln Pro Pro Lys Glu Pro His Met Leu Phe Asp Arg
        115                 120                 125
Ile Arg Leu Val Val Thr Lys Gly Phe Ser Gly Thr Pro Gly Ser Asn
    130                 135                 140
Glu Asn Ser Thr Gln Asn Val Tyr Lys Ile Pro Pro Thr Thr Thr Lys
145                 150                 155                 160
Ala Leu Cys Pro Leu Tyr Thr Ser Pro Arg Thr Val Thr Gln Ala Pro
                165                 170                 175
Pro Lys Ser Thr Ala Asp Val Ser Thr Pro Asp Ser Glu Ile Asn Leu
            180                 185                 190
Thr Asn Val Thr Asp Ile Ile Arg Val Pro Val Phe Asn Ile Val Ile
        195                 200                 205
Leu Leu Ala Gly Gly Phe Leu Ser Lys Ser Leu Val Phe Ser Val Leu
    210                 215                 220
Phe Ala Val Thr Leu Arg Ser Phe Val Pro
225                 230
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